Strategies for improving long-term renal transplant outcome

Valorisation addendum

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Relevance

In the first part of this thesis we demonstrated that conversion from cyclosporin (CsA) to tacrolimus (Tac) resulted in improvement of lipid, eGFR, and blood pressure in renal recipients even long after renal transplantation. These factors are related to cardiovascular disease, graft survival and death. Improvement of these factors will result on the long term in an improvement in patient and graft survival and less cardiovascular comorbidity.
As recipients of a renal transplant have, in general, a better quality of life than dialysis patients, a longer functioning graft will also result into more Quality-adjusted life years (Qualy's).
Every delay of dialysis is cost effective, since the cost of dialyses is on an average € 55000 per year, and the costs of nephrologic care of a donor recipients is € 8000 every year after the first year. So every additional year of graft survival stands for a saving of € 47000,-. (costs are adapted from the Dutch Transplantation Society)
Less cardiovascular comorbidity is also related to better quality of live and, because of less treatments and investigations, savings of money.
The improvement of lipids and blood pressure will result in less prescribed medication (and thus saves money). As adherence (taking the medication) is related to the number of drugs to be ingested,[1,2] this will also result into an improved adherence to immunosuppression. Thereby contributing to improvement in graft survival. It is stated that non-adherence to immunosuppression is one of the main causes of late immunological graft failure.[3]
After conversion from CsA to Tac, there is no need to use steroids in low and intermediate risk patients for maintenance therapy. Withdrawal of steroids also leads to improvement of lipids and improvement of blood pressure with the same advantages on cardiovascular disease and prescription costs as described above.
Furthermore, skipping the steroids will lead to a lower incidence of diabetes mellitus, and also other disadvantages of steroid use, e.g. such a osteoporosis and gastric ulcers do not occur and therefore there is no need any more for prophylactic medicine. Bisphosphonates and proton pump inhibitors can be stopped, again with the benefit of improvement of adherence and lower costs.

In contrast to the general opinion, we have shown in Chapter 2, that there is no increased risk for DM after conversion from CsA to Tac monotherapy, not even after long-time exposure. So, there hardly any reason not to continue or medication with worse cardiovascular side effects because of the fear of DM during exposure to Tac. In the past it has been suggested that indeed cardiovascular mortality was lower in patients on Tac compared to CsA.[4]

In the second part of this thesis we demonstrate that the choice of immunosuppressive regimen matters in terms of progression of IF/TA during the first year post transplant and that is related to a better eGFR at that time (Chapter 6). Therefore a pre-transplant biopsy of the donor kidney may guide the immunosuppressive regimen for a given recipient. A better eGFR is in general related to less cardiovascular comorbidity/mortality and an improved graft survival with all its benefits mentioned earlier.

Loss of Peritubular Capillaries (PTC's) is studied in Chapter 7 for the first time early post-transplant. Loss of PTC's observed at month 3 is related to donor type (more in post-mortal donors, especially DCD), rejection, donor age and number PTC's at implantation. The results of this (pilot-)study have to be confirmed in further studies, but suggest that this may be a surrogate end-point in studies on prevention of ischemia-reperfusion damage by shortening the ischemia times and may be used in studies on newer preservation techniques (e.g. machine preservation, warm preservation, oxygenated preservation).

Target groups

First our results are of interest for our patients, the kidney recipients. Second these result are also of interest for our nephrologic colleagues who work in the peripheral hospitals. They see their patients after the first year after renal transplantation and take care of the cardiovascular risk factors/comorbidity. Third, these results are of interest for academic medical specialists and researchers, especially the second part of the thesis about IF/TA and loss of PTC's

Activities

Our findings suggest that histologic assessment of a pre-implantation biopsy may guide the choice of immunosuppression to maximize transplant survival. When histologic assessment of a pre-implantation biopsy is not possible for logistic reasons, this choice must be made on clinical experience including 'donor source' and 'donor age'. Currently, we are investigating this item in more detail in a large study supported by a grant from the Dutch Kidney Foundation.
Loss of PTC in renal biopsies might be an early marker of IF/TA. Progression of PTC loss is correlated with ischemia/reperfusion damage and related to longer ischemic periods around donation and transplantation. Because of better logistics, the cold ischemic time in our center is decreased over the recent years. Moreover, also improvement in renal preservation (e.g. by machine perfusion, oxygenation, warm perfusion) may reduce ischemia/reperfusion damage and preserve PTC's. Currently, we investigate if loss of PTC's is indeed less in kidneys who were transplanted after machine-

preservation compared to cold-storage (retrospective analysis of data from a large RCT).
The use of protocol biopsies including measurement of PTC loss may be an useful early tool and a surrogate marker for progression of IF/TA and worse graft survival. In donors PTC loss in the kidney predicts renal allograft function after one year. PTC loss in the kidney may match with the capillary rarefaction in skin or nail fold in donors, so that we can examine, non-invasive, the quality of the (living) donor before transplantation by using capillaroscopy of the nail folds and skin microvasculature.

References

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